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1	1	test adj1 compound near5 uracil adj2 misincorporation	USPAT; US-PGPUB; DERWENT	2003/05/21 15:01
2	8	uracil adj2 misincorporation	USPAT; US-PGPUB; DERWENT	2003/05/21 15:03
3	104	uracil and misincorporation	USPAT; US-PGPUB; DERWENT	2003/05/21 15:04
4	77	(uracil and misincorporation) and test	USPAT; US-PGPUB; DERWENT	2003/05/21 15:04
5	49	((uracil and misincorporation) and test) and compound	USPAT; US-PGPUB; DERWENT	2003/05/21 15:26
6	1	dUTPase same uracil-DNA adj1 glycosylase same Ugi	USPAT; US-PGPUB; DERWENT	2003/05/21 15:27
7	0	dUTPase near5 uracil-DNA adj1 glycosylase near5 Ugi	USPAT; US-PGPUB; DERWENT	2003/05/21 15:28
8	1	dUTPase and uracil-DNA adj1 glycosylase and Ugi	USPAT; US-PGPUB; DERWENT	2003/05/21 15:28

1: Oncol Res 1997;9(2):77-88 Related Articles, Links

Determinants of cytotoxicity with prolonged exposure to fluorouracil in human colon cancer cells.

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To explore the determinants of cytotoxicity during prolonged exposure to pharmacologically relevant concentrations of 5-fluorouracil (FUra), we studied the effects of FUra at concentrations ranging from 0.1 to 1 microM in HCT 116 and HT 29 colon cancer cells grown in the presence of physiologic levels of leucovorin. A 5- and 7-day exposure to 1 microM FUra reduced cell growth to 46% and 20% of control in HT 29 cells and to 74% and 38% of control in HCT 116 cells. Concurrent exposure to thymidine (10 or 20 microM) or uridine (1 mM) provided partial protection against FUra toxicity in HT 29 cells, but did not protect HCT 116 cells. After a 24-h exposure to 1 microM [3H]FUra, free 5-fluoro-2'-deoxyuridine-5' -monophosphate (FdUMP) and FUDP. + FUTP levels were 0.7 and 144 pmol/10(6) cells in HT 29 cells, respectively, and 3.9 and 178 pmol/10(6) cells in HCT 116 cells. FdUMP and FUDP + FUTP pools increased by 5.7- and 2.0-fold in HT 29 cells and by 1.7- and 3.3-fold in HCT 116 cells over the next 48 h, but did not accumulate thereafter. After a 24-h exposure to 1 microM [3H]FUra, FUra-RNA levels were 158 and 280 fmol/microgram in HT 29 and HCT 116 cells, respectively; FUra-RNA levels increased over time, and reached 700 and 1156 fmol/microgram at day 5. Concurrent exposure to 1 mM uridine for 72 h did not diminish [3H]FUra-RNA incorporation. Upon removal of [3H]FUra following a 24-h exposure, FUra-RNA levels remained relatively stable with 57-78% retained at 120 h. A low level of [3H]FUra-DNA incorporation was detected in HT 29 cells. Thymidylate synthase (TS) catalytic activity in control cells was 2-fold higher in HCT 116 cells compared to HT 29 cells (47 vs. 23 pmol/min/mg). Total TS content increased 1.5- to 3-fold over control in both cell lines during FUra exposure, and ternary complex formation was evident for up to 96 h-dTTP pools were not depleted in FUra-treated cells, suggesting that residual TS catalytic activity was sufficient to maintain dTTP pools relative to demand. Surprisingly, the partial inhibition of TS was accompanied by a striking accumulation of immunoreactive "dUMP" pools in both lines; dUTP pools also increased 2-to 3-fold. In summary, the gradual and stable accumulation of FUra in

RNA noted in both lines may account for the thymidine-insensitive component of FUra toxicity. Because dTTP pools were not appreciably diminished, the interference with nascent DNA chain elongation and induction of single-strand breaks in newly synthesized DNA in both cell lines may be due to misincorporation of deoxyuridine nucleotides.

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